

TRAUMATISMO CRANEOENCEFÁLICO COMO ENTIDAD FISIOPATOLÓGICA COMPLEJA. NUEVOS AVANCES EN EL DIAGNÓSTICO Y EL TRATAMIENTO:

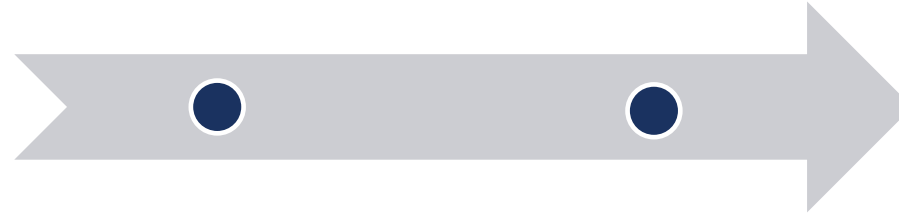
BIOMARCADORES SÉRICOS

Molés Pérez P., Quirós Martí M., Vega Torres E.H.,
Tabarés Palacín D., Quilis-Quesada V.



❖ TCE = entidad compleja → **FACTORES PRONÓSTICOS**

ANÁLISIS GLOBAL



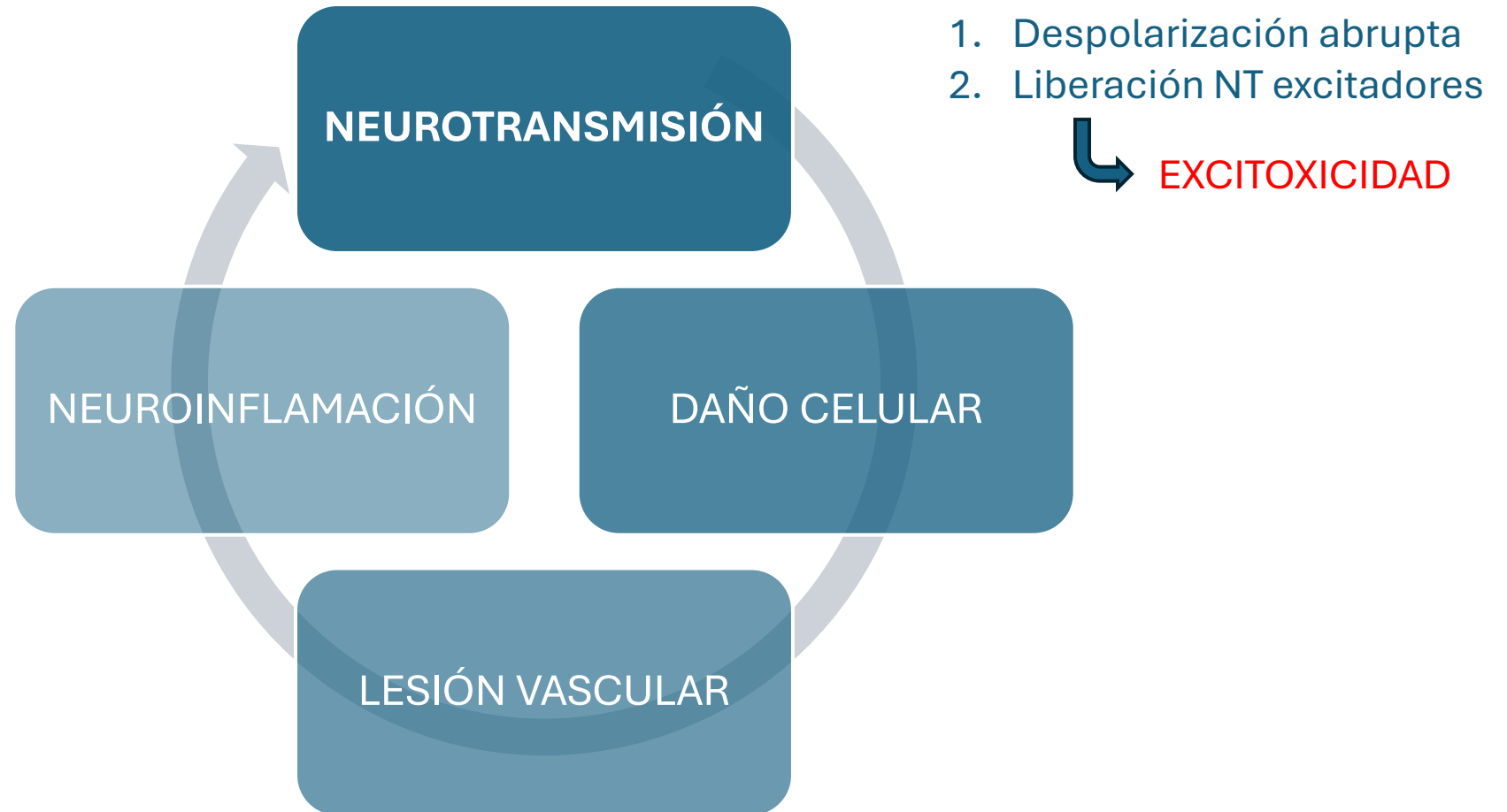
TOMA DE DECISIONES

CLASIFICACIÓN DE FACTORES

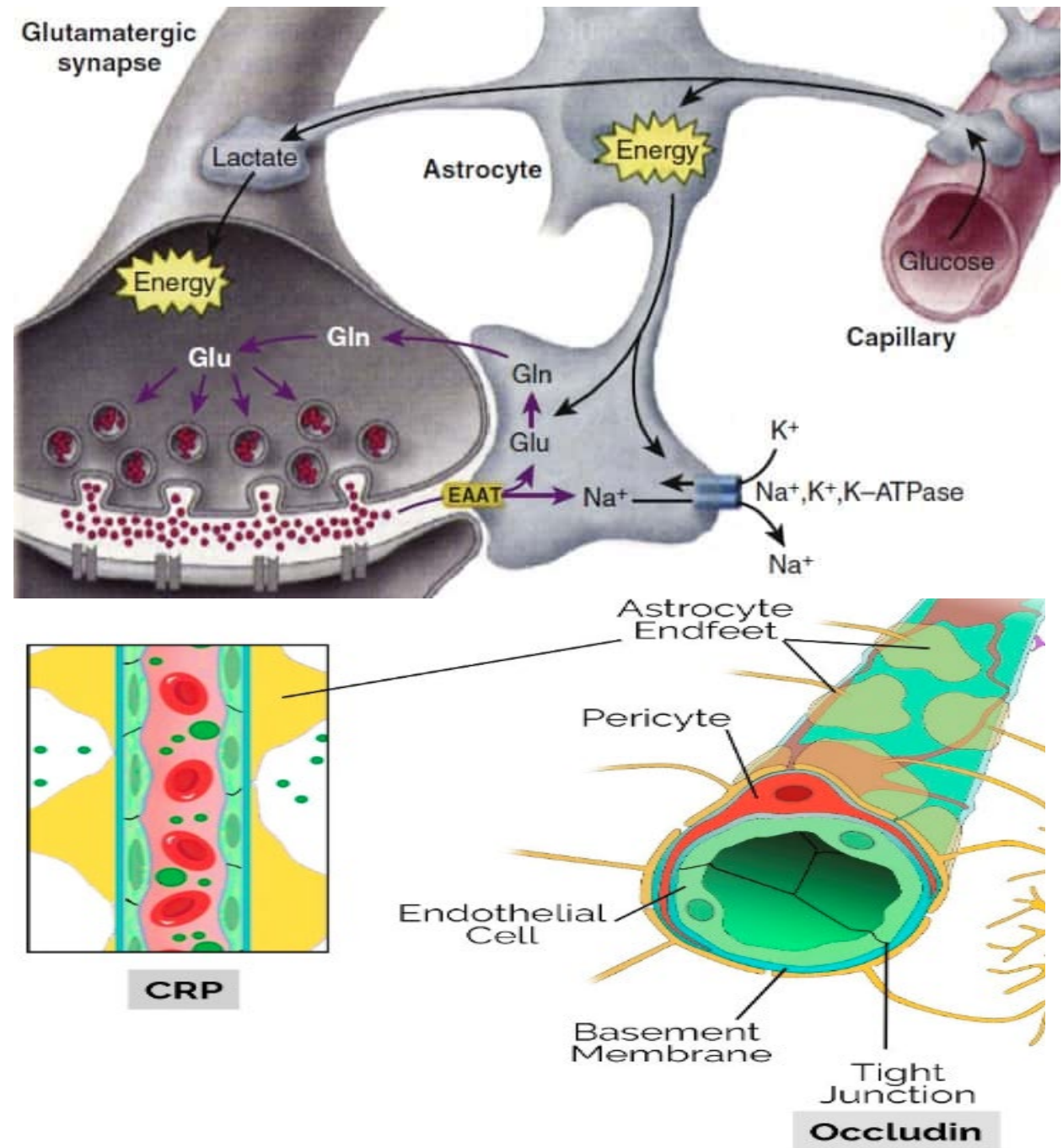
CLÁSICOS Validados	NUEVOS En investigación
Edad → ¿Ancianos! + función basal + ¿ACO?	Monitorización multimodal (PIC, PtO2)
Sexo	BIOMARCADORES SÉRICOS
GCS admisión / pupilas	
Estado neurológico previo	
Tiempo	Densitometría y pérdida de diferenciación sustancia gris-blanca en TC
Hallazgos en TC. * Volumen (ml) * Grosor (mm) * Desplazamiento LM (mm) * Lesiones * Pérdida * Herniaciones	Radiómica aplicada al TC inicial

FISIOPATOLOGÍA

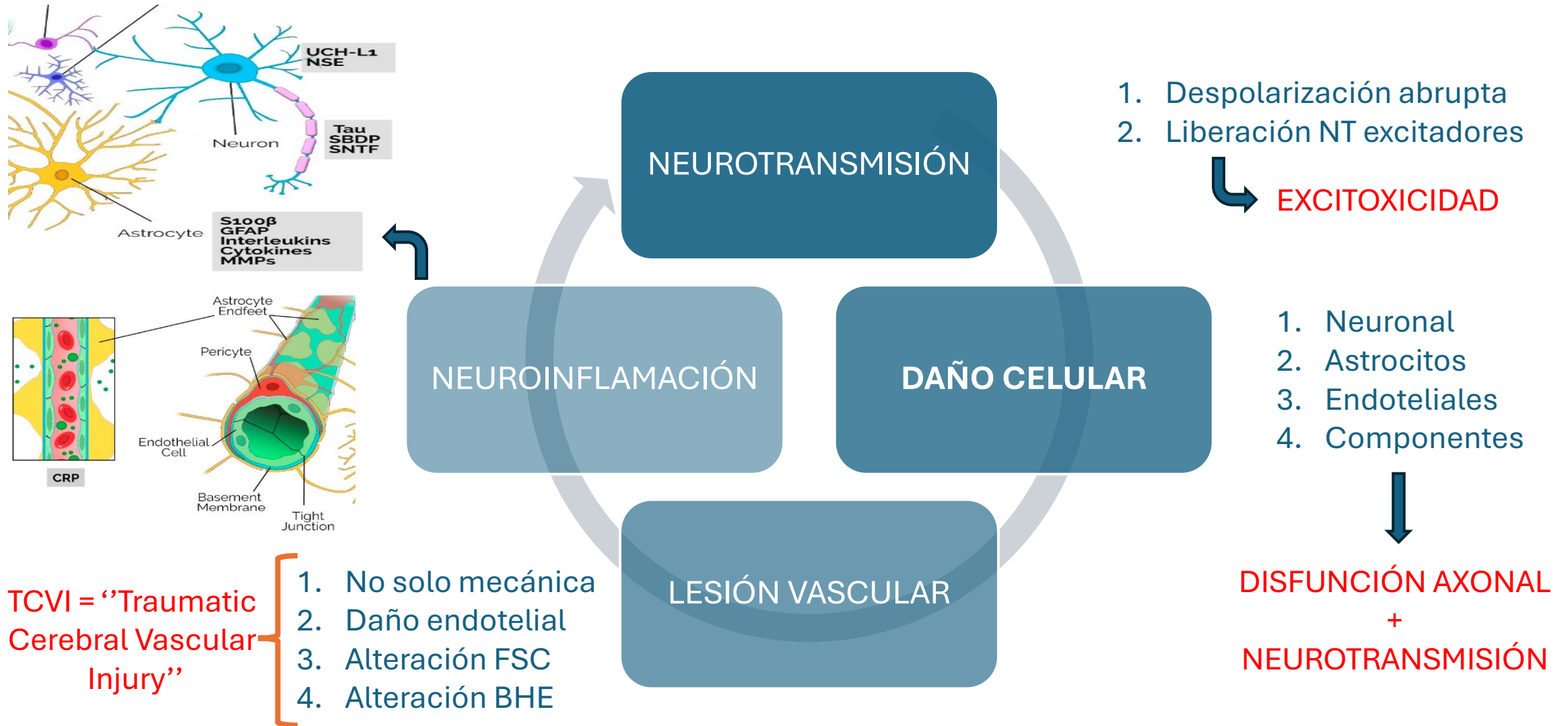
MODELO DE LA CASCADA NEUROMETABÓLICA



1. Hiperglicólisis = aumento de lactato
2. Daño membrana celular
3. Disfunción mitocondrial
4. Estrés oxidativo
5. Muerte celular



MODELO DE LA CASCADA NEUROMETABÓLICA



“Todos estos procesos condicionan la liberación de proteínas específicas del SNC al LCR y, secundariamente, a la sangre, lo que constituye la base fisiopatológica para el empleo de biomarcadores en el TCE”.

BIOFLUIDOS DISPONIBLES

SANGRE

LCR

El más estudiado

Menos estudios

Auge técnicas de análisis

Menor disponibilidad

Buen poder de detección

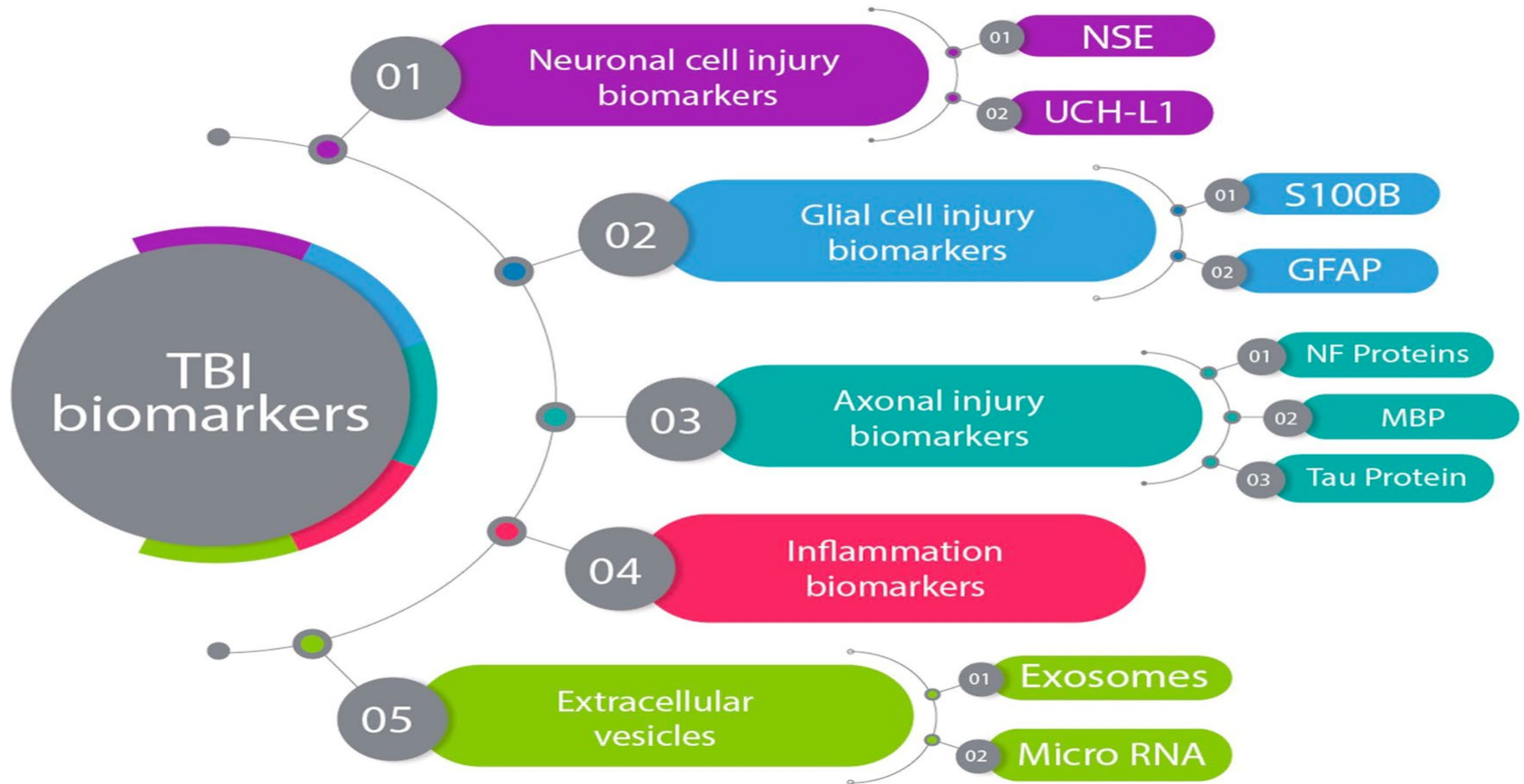
Mayor poder de detección

Relativo bajo coste

Mayor coste

Extracción tolerable

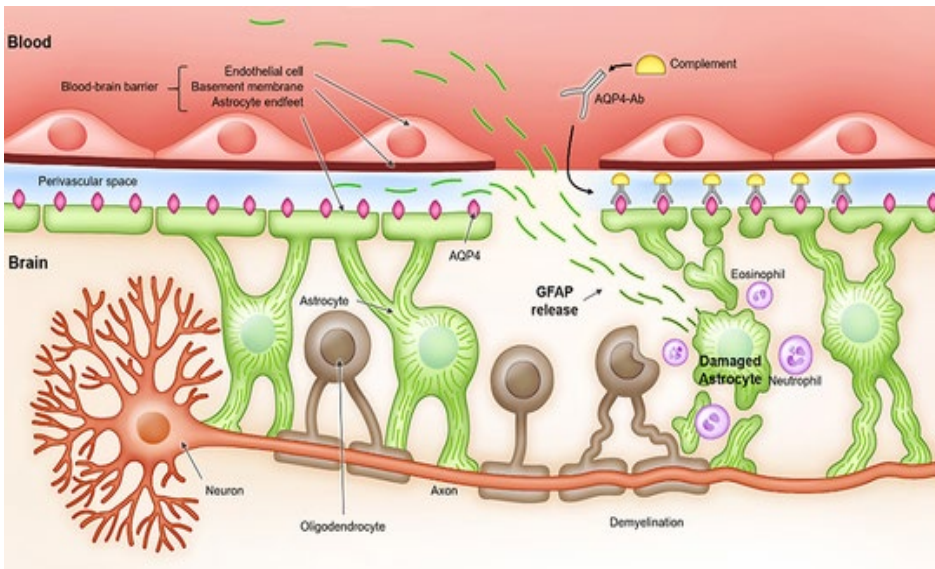
Más invasivo



BIOMARCADOR	Origen celular	Tiempo	Qué indica	Limitaciones
GFAP (<i>Glial Fibrillary Acidic Protein</i>)	Astrocitos	Muy precoz (1–6 h)	Daño glial; severidad de lesión; mortalidad	Específico de glía, pero no distingue lesión focal vs difusa
UCH-L1 (<i>Ubiquitin C-terminal Hydrolase L1</i>)	Neuronas (cuerpo celular, axones)	Precoz (1–12 h)	Daño neuronal directo; volumen hematoma; mal desenlace	Se eleva también en ictus y neurodegeneración
S100B	Astrocitos, células de Schwann	Precoz (horas)	Discriminación lesión leve; pronóstico funcional	Elevado en trauma extracraneal y melanoma
NSE (<i>Neuron Specific Enolase</i>)	Neuronas, células neuroendocrinas	Pico 24–48 h	Daño neuronal; mal pronóstico en TBI grave	Aumenta en hemólisis y neoplasias
Tau (<i>fosforilada</i>)	Axones	Subagudo (días)	Lesión axonal difusa; deterioro cognitivo	No específico de trauma (también en Alzheimer, CTE)
NfL (<i>Neurofilamento ligero</i>)	Axones	Precoz, pero persiste semanas–meses	Lesión axonal; pronóstico funcional a largo plazo	Elevado en enfermedades neurodegenerativas
Otros en investigación (<i>IL-6, miRNAs, metabolómica</i>)	Inflamación sistémica, expresión génica	Variable	Modulación inflamatoria; predicción de evolución	Aún experimentales

GFAP = “Glial Fibrillary Acidic Protein”

BIOMARCADOR	Origen celular	Tiempo	Qué indica	Limitaciones
GFAP (Glial Fibrillary Acidic Protein)	Astrocitos	Muy precoz (1–6 h)	Daño glial; severidad de lesión; mortalidad	Específico de glía, pero no distingue lesión focal vs difusa



A Literature Review of Traumatic Brain Injury Biomarkers

Hazem S. Ghaith¹ · Asmaa Ahmed Nawar² · Mohamed Daa Gabra³ · Mohamed Essam Abdelrahman³ · Mohamed H. Nafady⁴ · Eshak I. Bahbah⁵ · Mahmoud Ahmed Ebada^{2,6} · Ghulam Md Ashraf^{7,8} · Ahmed Negida^{2,9} · George E. Barreto¹⁰

Received: 3 December 2021 / Accepted: 30 March 2022 / Published online: 30 April 2022



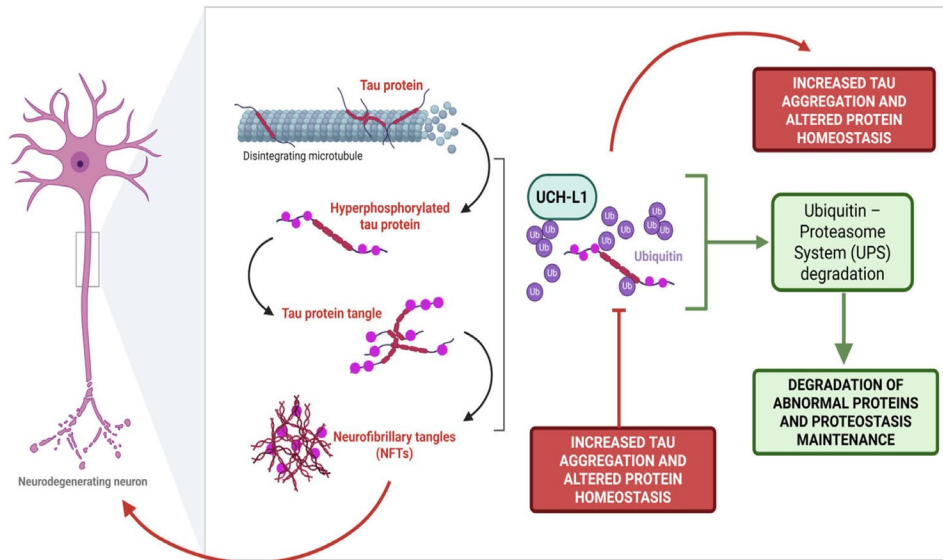
1. Filamento intermedio en células astrocitarias
2. Soporte estructural neuronal
3. Activación de neuroglia
4. TCE → mayor activación



GLIOSIS
AUMENTA EXPRESIÓN

UCH-L1 = ‘Ubiquitin C-terminal Hydrolase L1’

BIOMARCADOR	Origen celular	Tiempo	Qué indica	Limitaciones
UCH-L1 (Ubiquitin C-terminal Hydrolase L1)	Neuronas (cuerpo celular, axones)	Precoz (1–12 h)	Daño neuronal directo; volumen hematoma; mal desenlace	Se eleva también en ictus y neurodegeneración



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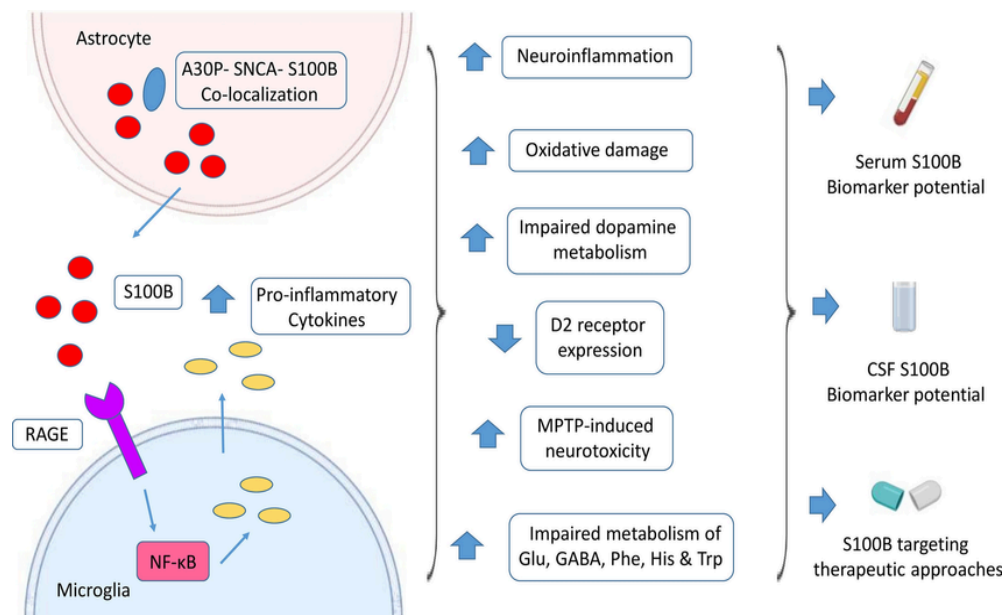
1. Enzima proteolítica citoplasmática
2. Eliminación proteínas anómalas
3. Fisiológico + patológico



ROTURA BHE
AUMENTA EXPRESIÓN

S100B

BIOMARCADOR	Origen celular	Tiempo	Qué indica	Limitaciones
S100B	Astrocitos, células de Schwann	Precoz (horas)	Discriminación lesión leve; pronóstico funcional	Elevado en trauma extracraneal y melanoma



A Literature Review of Traumatic Brain Injury Biomarkers

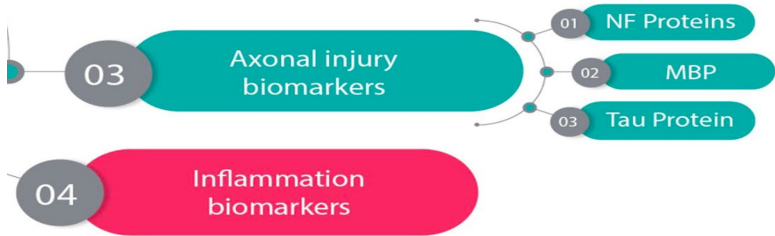
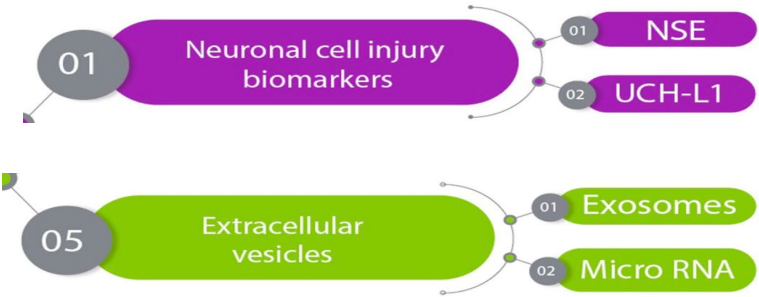
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1. Calcium binding protein
2. TCE/ischemia
3. Activación neuroglia
4. Difunde CSF → sangre

OTROS

BIOMARCADOR	Origen celular	Tiempo	Qué indica	Limitaciones
<i>NSE (Neuron Specific Enolase)</i>	Neuronas, células neuroendocrinas	Pico 24–48 h	Daño neuronal; mal pronóstico en TBI grave	Aumenta en hemólisis y neoplasias
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Otros en investigación (IL-6, miRNAs, metabolómica)	Inflamación sistémica, expresión génica	Variable	Modulación inflamatoria; predicción de evolución	Aún experimentales



BAJA ESPECIFICIDAD

EVIDENCIA CLÍNICA

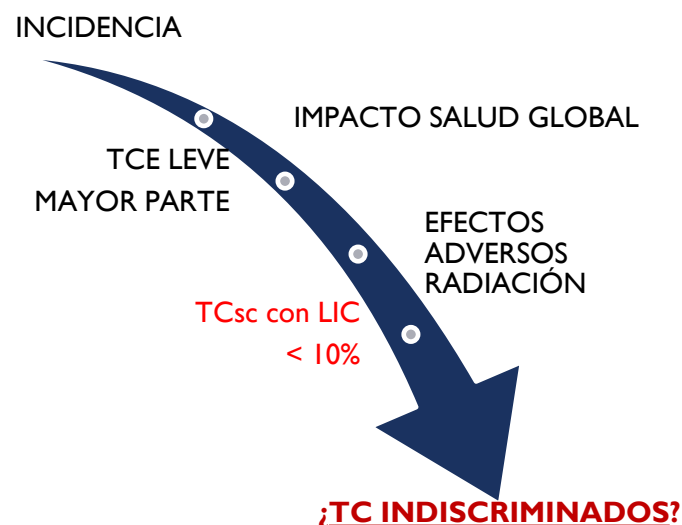
Y

APLICACIÓN PRÁCTICA

Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study

Jeffrey J Bazarian, Peter Biberthaler*, Robert D Welch, Lawrence M Lewis, Pal Barzo, Viktoria Bogner-Flatz, P Gunnar Brodin, Andras Büki, James Y Chen, Robert H Christenson, Dallas Hack, J Stephen Huff, Sandeep Johar, J Dedrick Jordan, Bernd A Leidel, Tobias Lindner, Elizabeth Ludington, David O Okonkwo, Joseph Ornato, W Frank Peacock, Kara Schmidt, Joseph A Tyndall, Arastoo Vossough, Andy S Jagoda*

An estimated 54–60 million people worldwide sustain a traumatic brain injury (TBI) each year.¹ In the USA, TBI results in more than 2.5 million emergency department visits annually, most of these being mild TBI (also known as concussion).² Head CT scan is the diagnostic modality of choice to evaluate patients for traumatic intracranial injuries,³ contributing to the approximately 20 million head CT scans performed annually in the USA.⁴ Although effective for detecting traumatic injuries that require observation or neurosurgical evacuation, the widespread use of head CT scanning has been questioned due to potential adverse effects of radiation exposure, unnecessary emergency department resource use, and cost.^{4–6} These factors take on added importance for patients with mild TBI in whom the prevalence of



CT-detected intracranial injury is typically less than 10%.⁶ Clinical decision rules (CDRs) have been developed with the goal of reducing unnecessary head CT scans, but they have had only modest impact on CT use.^{5,7}

Prior studies have shown the potential for blood-based brain injury biomarkers to predict the absence of intracranial injury after TBI and aid in reducing unnecessary head CT use.^{8–11} Of the many different proteins, small molecules, and lipid products investigated in humans for this purpose, the S100 astroglial calcium-binding protein B (S100B) has been the most studied. Although some guidelines have recommended this biomarker for clinical use to predict intracranial injury on CT,¹² the 2008 American College of Emergency Physician guidelines for managing adult patients with mild TBI determined that use of S100B only had level C

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evidence.³ Currently, no blood-based brain biomarker tests in the USA have been approved by the US Food and Drug Administration (FDA) for use outside a research setting. This gap in diagnostic capability has received much attention with many calls for advancing brain biomarker research.¹³

Several novel brain proteins have been identified that potentially address this gap.¹⁴ Two proteins, ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), have emerged as promising candidates for translation to clinical use. Preliminary

We therefore did a large, prospective, multicentre trial, entitled A Prospective Clinical Evaluation of Biomarkers of Traumatic Brain Injury (ALERT-TBI), aiming to validate the ability of a biomarker test combining UCH-L1 and GFAP, at predetermined cutoff values, to predict traumatic intracranial injuries on head CT scan within 12 h of TBI.



1. FALTA DE ESTUDIOS
2. GFAP + UCH-L1



ALERT-TBI

ASPECTOS TÉCNICOS

OBJETIVO

Predicción de LIC
en TC cerebral
< 12h de TCE

Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study

Jeffrey J Bazarian*, Peter Biberthaler*, Robert D Welch, Lawrence M Lewis, Pal Barzo, Viktoria Bogner-Flatz, P Gunnar Brolinson, Andras Büki, James Y Chen, Robert H Christenson, Dallas Hack, J Stephen Huff, Sandeep Johar, J Dedrick Jordan, Bernd A Leidel, Tobias Lindner, Elizabeth Ludington, David O Okonkwo, Joseph Ornato, W Frank Peacock, Kara Schmidt, Joseph A Tyndall, Arastoo Vossough, Andy S Jagoda

Outcomes

1. El uso conjunto de GFAP y UCH-L1 para la predicción de LIC en TC presenta una sensibilidad diagnóstica del 0,976 y un VPN del 0,996. Destaca este último: **valores negativos** = no elevados implican una predicción del 99,6% de no encontrar LIC en TC.

we determined UCH-L1 and GRP test specificity, 22.2 pg/mL; $p < 0.0001$; median UCH-L1 604.8 pg/mL vs. positive predictive value (PPV) and likelihood ratio

2. Los valores de GFAP y UCH-LI se vieron **claramente elevados** respecto al valor inferior del rango en los pacientes con LIC, con **medianas de 135 pg/ml** (VS 22 pg/ml) para GFAP y de **604,8 pg/ml** (VS 261 pg/ml) para UCH-LI.

S = 0.976

VPN = 0.996

The game changer: UCH-L1 and GFAP-based blood test as the first marketed in vitro diagnostic test for mild traumatic brain injury

Firas Kobeissy, Rawad Daniel Arja, Jennifer C. Munoz, Deborah A. Shear, Janice Gilsdorf, Jiepei Zhu, Hamad Yadikar, William Haskins, J. Adrian Tyndall & Kevin K. Wang

1. ESPECÍFICOS
2. SENSIBLES
3. DETECTABLES
4. NIVELES LCI > SANOS
5. CORRELACIÓN

Currently, UCH-L1/GFAP are considered the first-generation biomarkers for TBI and other forms of brain injury, these biomarkers have paved the way for new biomarkers to follow [2,7]. Most importantly, the criteria for a promising new TBI

biomarker depends on [1] brain specificity or enrichment [2], robust detectability in blood following injury, and [3] sensitivity high enough to detect mild injury. New biomarker discov-

According to Wang et al. [10], the ideal and reliable fluid biomarker of TBI should meet the following criteria: (1) First, head trauma should induce the release of that biomarker into accessible body fluids; (2) the biomarker level must increase significantly in TBI patients than in healthy people; (3) the biomarker should correlate quantitatively and qualitatively with injury severity; and (4) the level of the biomarker should be associated with other clinical diagnostic tools as GCS, CT, and MRI [10].

Study protocol for investigating the clinical performance of an automated blood test for glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase L1 blood concentrations in elderly patients with mild traumatic BRAIN Injury and reference values (BRAINI-2 Elderly European study): a prospective multicentre observational study

Alfonso Lagares,^{1,2,3} Jean-François Payen,^{4,5} Peter Biberthaler,⁶ M Antonia Poca,⁷ Odile Méjan,⁸ Vladislav Pavlov,⁹ Damien Viglino,^{10,11} Vincent Sapin,¹² Aurora Lassaletta,¹³ Javier de la Cruz,¹⁴ Braini2_elderly_investigators Collaborative group¹⁵

will assess the performance of an automated test for measuring serum GFAP and UCH-L1 in elderly patients to predict the absence of intracranial lesions on head CT scans after mTBI, and determine both biomarkers reference values in a non-TBI elderly population.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a large multicentre prospective study to validate the value of serum biomarkers, glial fibrillar acidic protein and ubiquitin carboxy-terminal hydrolase L1, concentrations for predicting brain CT findings after mild traumatic brain injury (mTBI) in the elderly population most commonly affected by mild TBI.
- ⇒ Comorbidities will be considered but will not prevent patient inclusion, making the sample similar to real-world data.
- ⇒ Comorbidities' effect on the concentrations of these blood biomarkers will be assessed.
- ⇒ Reference values for these biomarkers will also be obtained in a large group of non-TBI patients, helping fine-tune the test's value.
- ⇒ Variability in the indications of CT scans can influence their positivity rate across countries and centres, thereby influencing the study's statistical power.

Performance of glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) biomarkers in predicting CT scan results and neurological outcomes in children with traumatic brain injury (BRAINI-2 paediatric study): protocol of a European prospective multicentre study

Fleur Lorton,¹ Alfonso Lagares,² Javier de la Cruz,³ Odile Méjan,⁴ Vladislav Pavlov,⁵ Vincent Sapin,⁶ Maria Antonia Poca,^{7,8} Markus Lehner ,⁹ Peter Biberthaler,¹⁰ Anne Chauviré-Drouard,¹ Christèle Gras-Le-Guen,¹ Pauline Scherdel ,¹
BRAINI-2 paediatric Collaborative group

Introduction In light of the burden of traumatic brain injury (TBI) in children and the excessive number of unnecessary CT scans still being performed, new strategies are needed to limit their use while minimising the risk of delayed diagnosis of intracranial lesions (ICLs). Identifying children at higher risk of

1. EXPLORACIÓN NRL
2. VALORES DE REFERENCIA
3. MENOS TC

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The multicentre design of the study with broad prospective recruitment in several European countries and the wide spectrum of clinical presentations of the patients included will ensure the generalisability of our findings.
- ⇒ The precision of the primary outcome measurement will be ensured through evaluation of CT images by two independent neuroradiological experts.
- ⇒ The follow-up of the included children will enable confirmation of the absence of intracranial lesions, which may have been detected postdischarge from the emergency department.
- ⇒ As performing a CT scan for patient management is not mandatory as an inclusion criterion, not all children included will ultimately be considered in the main analysis, as the primary outcome measure will be the CT scan result.

POTENCIAL FUTURO

CONCLUSIONES

Guía para el manejo del TCE

Servicio de Urgencias

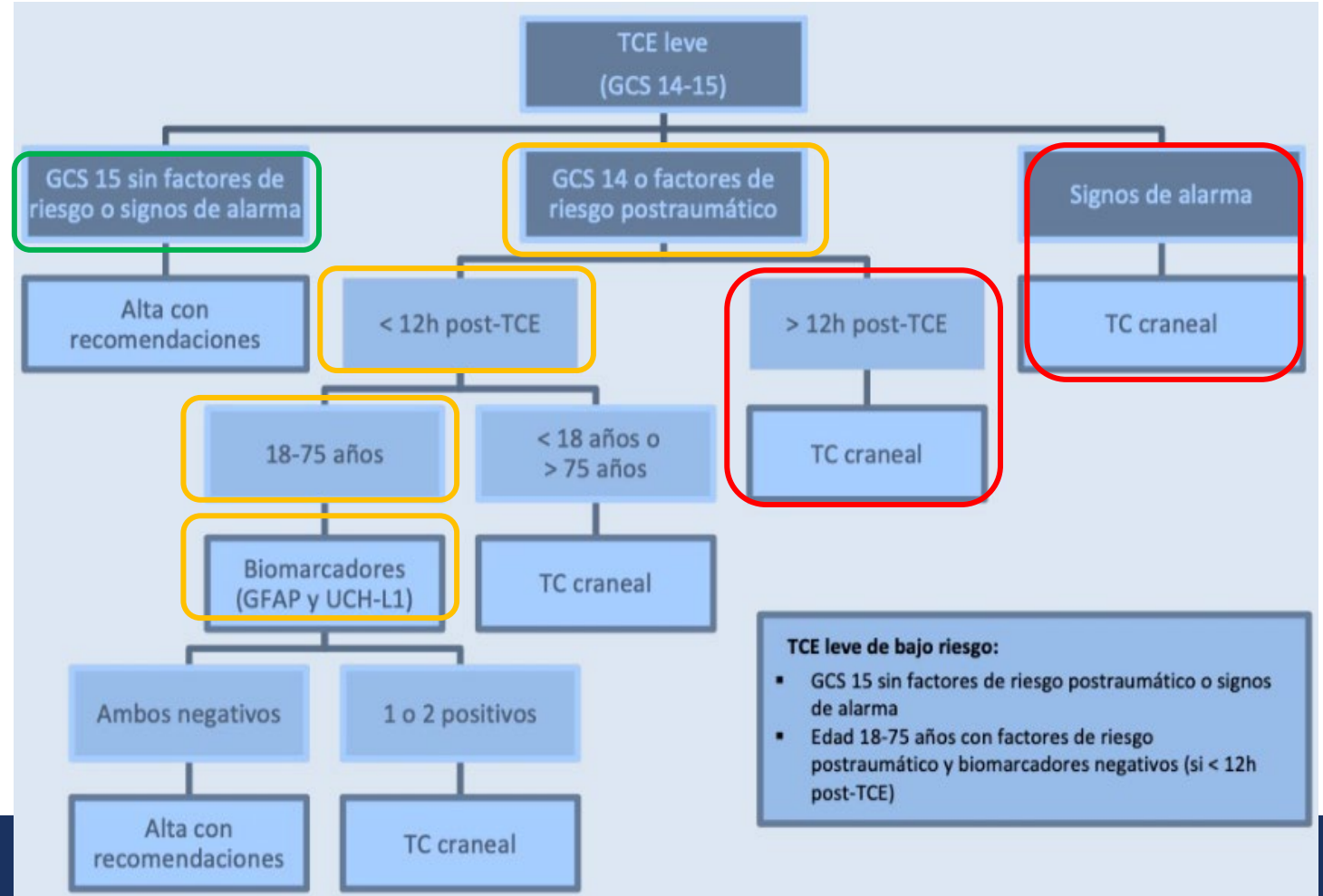
URGENCIAS
CLÍNICO
VALENCIA

AUTORES:

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Lorena Cifuentes García
Fernando Benlloch Llopis

Protocolo consensuado con los Servicios de:

Anestesiología y Reanimación
Laboratorio
Neurocirugía
Neurología
Radiodiagnóstico



1. Predicción **PRONÓSTICA** de lesiones intracraneales en TC cerebrales que ayuden en el **manejo inicial** y en la **toma de decisiones** para el tratamiento médico, quirúrgico o conservador/limitador = **¡CURVAS!**

2. Predicción en la **EVOLUCIÓN** de lesiones:

- a. Pacientes en GCS15 con lesiones que potencialmente pueden llevar a deterioro neurológico inminente en horas-días.
- b. ¿Vigilancia neurológica más estrecha?
- c. ¿Plantear pruebas de imagen de control previamente a las 24h?
- d. ¿Plantear medidas más invasivas de monitorización neurológica?

NEUROCRÍTICOS + CUIDADOS EN UNIDADES DE INTENSIVOS

CONCLUSIONES

1. **GFAP y UCH-L1** se constituyen como los biomarcadores más validados y cercanos a la práctica clínica diaria, abriendo la puerta al estudio de sus múltiples utilidades y también a otros biomarcadores futuros.
2. Los **factores clásicos** (edad, GCS, pupilas, comorbilidad, anticoagulación, midline shift) siguen siendo los **pilares** para la toma de decisiones inmediatas y establecer el pronóstico.
3. En el futuro podríamos pasar de decisiones basadas en “solo” clínica + TC, a **modelos multimodales más precisos y personalizados**.
4. Las **herramientas emergentes** (biomarcadores séricos, radiología cuantitativa, monitorización multimodal) representan un gran avance para el manejo de una entidad compleja como es el TCE y prometen mejorar la estratificación pronóstica y la selección terapéutica en los próximos años.



II Edition

MICRONEUROSURGICAL & ENDOSCOPIC HANDS-ON COURSE

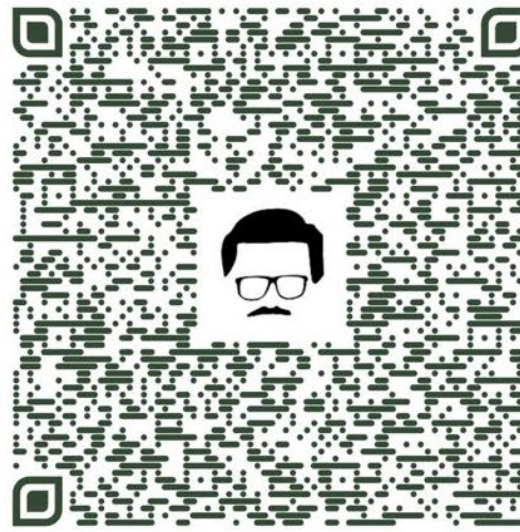


ANATOMY APPLIED TO NEUROSURGERY

THE EVANDRO DE OLIVEIRA LEGACY 

University Clinical Hospital of Valencia, Spain

June 27th - July 2nd 2026



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